WEST Search History

DATE: Wednesday, October 15, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB; PLUR=YES; OP=ADJ		
L16	l10 and l9	1	L16
L15	L14 and l9	0	L15
L14	L10 and @ad<20010119	2	L14
L13	L12 and @ad<20010119	0	L13
L12	L11 and (protein or peptide)	4	L12
L11	l10 and inhibit$7	4	L11
L10	separase or proteinase esp1 or sister separating separin	6	L10
L9	L8 or l7 or l6 or l5 or l4 or l3 or l2 or l1	12689	L9
L8	(((530/300)!.CCLS.))	2798	L8
L7	(((435/219)!.CCLS.))	877	L7
L6	(((435/212)!.CCLS.))	758	L6
L5	(((435/195)!.CCLS.))	521	L5
L4	(((435/183)!.CCLS.))	4009	L4
L3	(((435/23)!.CCLS.))	834	L3
L2	(((435/18)!.CCLS.))	883	L2
L1	((435/4)!.CCLS.)	3634	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. Document ID: US 6020151 A

L14: Entry 1 of 2 File: USPT Feb 1, 2000

US-PAT-NO: 6020151
DOCUMENT-IDENTIFIER: US 6020151 A

TITLE: Process for the production of 7-ADCA via expandase activity on penicillin G

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw Desc | Image

☐ 2. Document ID: US 5731165 A

L14: Entry 2 of 2 File: USPT Mar 24, 1998

US-PAT-NO: 5731165
DOCUMENT-IDENTIFIER: US 5731165 A

TITLE: Process for the production of 7-ADCA via expandase activity on penicillin G

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw Desc | Image

Generate Collection | Print

Terms	Documents
L10 and @ad<20010119	2

Display Format: - Change Format

Previous Page Next Page

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 6 of 6 returned.

☐ 1. Document ID: US 20030148462 A1

L10: Entry 1 of 6 File: PGPB Aug 7, 2003

PGPUB-DOCUMENT-NUMBER: 20030148462
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030148462 A1

TITLE: Dual inhibition of sister chromatid separation at metaphase

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20030083261 A1

L10: Entry 2 of 6 File: PGPB May 1, 2003

PGPUB-DOCUMENT-NUMBER: 20030083261
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030083261 A1

TITLE: Class of 12mer peptides that inhibit the function of the mitotic check point protein Mad2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20020164620 A1

L10: Entry 3 of 6 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020164620
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020164620 A1

TITLE: Method for identifying compounds modulating sister chromatid separation

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 4. Document ID: US 20020137018 A1

L10: Entry 4 of 6 File: PGPB Sep 26, 2002

PGPUB-DOCUMENT-NUMBER: 20020137018
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020137018 A1

TITLE: Securin is required for chromosomal stability in human cells

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

---

☐ 5. Document ID: US 6020151 A

L10: Entry 5 of 6 File: USPT Feb 1, 2000

US-PAT-NO: 6020151
DOCUMENT-IDENTIFIER: US 6020151 A

TITLE: Process for the production of 7-ADCA via expandase activity on penicillin G

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 6. Document ID: US 5731165 A

L10: Entry 6 of 6 File: USPT Mar 24, 1998

US-PAT-NO: 5731165
DOCUMENT-IDENTIFIER: US 5731165 A

TITLE: Process for the production of 7-ADCA via expandase activity on penicillin G

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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Generate Collection | Print

Terms	Documents
separase or proteinase esp1 or sister separating separin	6

Display Format: - Change Format

Previous Page Next Page

=> d his

(FILE 'HOME' ENTERED AT 12:36:40 ON 15 OCT 2003)

FILE 'REGISTRY' ENTERED AT 12:37:05 ON 15 OCT 2003
L1 1 S SEPARASE/CN

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 12:37:14 ON 15 OCT 2003

SEA L1

0*	FILE ADISCTI
0*	FILE AQUASCI
0*	FILE BIOCOMMERCE
28	FILE BIOSIS
0*	FILE CABA
10	FILE CANCERLIT
0*	FILE CAPLUS
0*	FILE CEABA-VTB
0*	FILE CONFSCI
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0*	FILE CROPU
0*	FILE DDFB
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0*	FILE DRUGB
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0*	FILE EMBAL
0*	FILE ESBIOBASE
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0*	FILE FOMAD
0*	FILE FOREGE
0*	FILE FROSTI
0*	FILE GENBANK
0*	FILE HEALSAFE
0*	FILE IFIPAT
0*	FILE KOSMET
0*	FILE LIFESCI
0*	FILE MEDICONF
49	FILE MEDLINE
0*	FILE NTIS
0*	FILE NUTRACEUT
0*	FILE OCEAN
0*	FILE PASCAL
0*	FILE PCTGEN
0*	FILE PHARMAML
0*	FILE PHIC
0*	FILE PHIN
0*	FILE RDISCLOSURE
0*	FILE SCISEARCH
11	FILE TOXCENTER
0*	FILE USPATFULL
0*	FILE USPAT2
0*	FILE VETB
0*	FILE VETU

L2 QUE L1

FILE 'MEDLINE, BIOSIS, TOXCENTER, CANCERLIT' ENTERED AT 12:38:41 ON 15 OCT 2003

FILE 'REGISTRY' ENTERED AT 12:38:47 ON 15 OCT 2003
SET SMARTSELECT ON
L3 SEL L1 1- CHEM : 5 TERMS
SET SMARTSELECT OFF

FILE 'MEDLINE, BIOSIS, TOXCENTER, CANCERLIT' ENTERED AT 12:38:48 ON 15 OCT 2003

L4 173 S L3
L5 63 S L4 (L) (INHIBIT?)
L6 31 DUP REM L5 (32 DUPLICATES REMOVED)
L7 10 S L6 AND PY<2002

=> d ibib ab 1-10

L7 ANSWER 1 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2001699704 MEDLINE
DOCUMENT NUMBER: 21614485 PubMed ID: 11747808
TITLE: Dual inhibition of sister chromatid separation at metaphase.
AUTHOR: Stemmann O; Zou H; Gerber S A; Gygi S P; Kirschner M W
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA.
CONTRACT NUMBER: GM26875-17 (NIGMS)
GM39023-08 (NIGMS)
HG00041 (NHGRI)
SOURCE: CELL, **(2001 Dec 14)** 107 (6) 715-26.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011219
Last Updated on STN: 20020125
Entered Medline: 20020117
AB Separation of sister chromatids in anaphase is mediated by **separase**, an endopeptidase that cleaves the chromosomal cohesin SCC1. **Separase** is **inhibited** by securin, which is degraded at the metaphase-anaphase transition. Using Xenopus egg extracts, we demonstrate that high CDC2 activity **inhibits** anaphase but not securin degradation. We show that **separase** is kept inactive under these conditions by a mechanism independent of binding to securin. Mutation of a single phosphorylation site on **separase** relieves the **inhibition** and rescues chromatid separation in extracts with high CDC2 activity. Using quantitative mass spectrometry, we show that, in intact cells, there is complete phosphorylation of this site in metaphase and significant dephosphorylation in anaphase. We propose that **separase** activation at the metaphase-anaphase transition requires the removal of both securin and an **inhibitory** phosphate.

L7 ANSWER 2 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2001542521 MEDLINE
DOCUMENT NUMBER: 21473267 PubMed ID: 11589568
TITLE: Role of the kinetochore protein Ndc10 in mitotic checkpoint activation in Saccharomyces cerevisiae.
AUTHOR: Fraschini R; Beretta A; Lucchini G; Piatti S
CORPORATE SOURCE: Dipartimento di Biotecnologie e Bioscienze, Universita degli Studi di Milano-Bicocca, Italy.
SOURCE: Mol Genet Genomics, **(2001 Sep)** 266 (1) 115-25.
Journal code: 101093320. ISSN: 1617-4615.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011009
Last Updated on STN: 20030208
Entered Medline: 20011025
AB Mitotic checkpoints delay cell cycle progression in response to alterations in the mitotic apparatus, thus ensuring correct chromosome segregation. While improper spindle orientation activates the Bub2/Bfa1-dependent checkpoint in budding yeast, delaying exit from mitosis, lack of bipolar kinetochore-microtubule attachment activates a signal transduction cascade that prevents both anaphase onset and exit from mitosis by **inhibiting** the Cdc20/APC (Anaphase Promoting Complex)-mediated proteolysis of securin and inactivation of mitotic cyclin-dependent kinases (CDKs), respectively. Proteolysis of the securin Pds1 is necessary to liberate the **separase** Esp1, which then triggers sister chromatid separation, whereas inactivation of mitotic CDKs is a prerequisite for exit from mitosis and for starting a new round of

DNA replication in the next cell cycle. In budding yeast, this latter checkpoint response involves the proteins Mad1, 2, 3, Bub1 and Bub3, whose vertebrate counterparts localize to unattached kinetochores. Mutations that alter other kinetochore proteins result in mitotic checkpoint activation, while the ndc10-1 mutation not only impairs kinetochore function, but also disrupts the checkpoint response, indicating a role for Ndc10 in this process. Here we present evidence that Ndc10 is not part of the Bub2/Bfa1-dependent pathway, and its role in the checkpoint response might also be different from that of the other Mad and Bub proteins. Indeed, Ndc10, unlike other mitotic checkpoint proteins, is not required for the mitotic block induced by overexpression of the Mps1 protein kinase, which is implicated in mitotic checkpoint control. Furthermore, the delay in mitotic exit caused by non-degradable Pds1, which does not require Mad and Bub proteins, depends on Ndc10 function. We propose that a pathway involving Ndc10 might monitor defects in the mitotic apparatus independently of the Mad and Bub proteins. Since the Esp1 **separase** is required for exit from mitosis in both ndc10-1 and nocodazole-treated mad2delta cells, the two signal transduction cascades might ultimately converge on the inactivation of Esp1.

L7 ANSWER 3 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2001534089 MEDLINE
DOCUMENT NUMBER: 21464657 PubMed ID: 11581162
TITLE: Drosophila separase is required for sister chromatid separation and binds to PIM and THR.
AUTHOR: Jager H; Herzig A; Lehner C F; Heidmann S
CORPORATE SOURCE: Department of Genetics, University of Bayreuth, 95440 Bayreuth, Germany.
SOURCE: GENES AND DEVELOPMENT, **(2001 Oct 1)** 15 (19) 2572-84.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011003
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Drosophila PIM and THR are required for sister chromatid separation in mitosis and associate in vivo. Neither of these two proteins shares significant sequence similarity with known proteins. However, PIM has functional similarities with securin proteins. Like securin, PIM is degraded at the metaphase-to-anaphase transition and this degradation is required for sister chromatid separation. Securin binds and **inhibits separase**, a conserved cysteine endoprotease. Proteolysis of securin at the metaphase-to-anaphase transition activates **separase**, which degrades a conserved cohesin subunit, thereby allowing sister chromatid separation. To address whether PIM regulates **separase** activity or functions with THR in a distinct pathway, we have characterized a Drosophila **separase** homolog (SSE). SSE is an unusual member of the **separase** family. SSE is only about one-third the size of other **separases** and has a diverged endoprotease domain. However, our genetic analyses show that SSE is essential and required for sister chromatid separation during mitosis. Moreover, we show that SSE associates with both PIM and THR. Although our work shows that **separase** is required for sister chromatid separation in higher eukaryotes, in addition, it also indicates that the regulatory proteins have diverged to a surprising degree, particularly in Drosophila.

L7 ANSWER 4 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2001471543 MEDLINE
DOCUMENT NUMBER: 21407745 PubMed ID: 11516952
TITLE: Securin is not required for cellular viability, but is required for normal growth of mouse embryonic fibroblasts.
AUTHOR: Mei J; Huang X; Zhang P
CORPORATE SOURCE: Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX 77030, USA.

SOURCE: CURRENT BIOLOGY, **(2001 Aug 7)** 11 (15) 1197-201.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010823
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Sister chromatid separation depends on the release of cohesion by the activity of Esp1, a member of the caspase family [1, 2]. In budding yeast, Esp1p is kept inactive by its association with Pds1p, until the onset of anaphase, when Pds1p is ubiquitinated by the APC/Cdc20 complex [3--5] and subsequently degraded by the 26S proteasome. Pds1 is not an essential gene in budding yeast, but is required for cell cycle arrest prior to anaphase in response to the disruption of spindle structures [6, 7]. Thus, Pds1 mutant yeast cells display precocious sister chromatid separation in the presence of nocodazole [6]. Mammalian orthologs of yeast Esp1 and Pds1, **separin** and securin, have been identified [8], and, as anticipated, a nondegradable mutant form of securin **inhibits** sister separation when added to mitotic Xenopus egg extracts [8]. Securin was also independently identified as PTTG (pituitary tumor transforming gene), a gene overexpressed in pituitary tumors [9]. The relationship between its overexpression in tumors and its control of sister chromatid cohesion remains ill defined. To explore securin function in mammals, we took a targeted gene disruption approach in mice. Here, we report that securin is neither essential for cell viability nor required for spindle checkpoint function, and mice lacking securin are viable and apparently normal, but mouse embryonic fibroblasts lacking securin grow abnormally in culture.

L7 ANSWER 5 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2001277712 MEDLINE
DOCUMENT NUMBER: 21264235 PubMed ID: 11371343
TITLE: Phosphorylation of the cohesin subunit Scc1 by Polo/Cdc5 kinase regulates sister chromatid separation in yeast.
AUTHOR: Alexandru G; Uhlmann F; Mechtler K; Poupart M A; Nasmyth K
CORPORATE SOURCE: Research Institute of Molecular Pathology (IMP), Dr Bohr-Gasse 7, A-1030, Vienna, Austria.
SOURCE: CELL, **(2001 May 18)** 105 (4) 459-72.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20030225
Entered Medline: 20010705

AB At the onset of anaphase, a caspase-related protease (**separase**) destroys the link between sister chromatids by cleaving the cohesin subunit Scc1. During most of the cell cycle, **separase** is kept inactive by binding to an **inhibitory** protein called securin. **Separase** activation requires proteolysis of securin, which is mediated by an ubiquitin protein ligase called the anaphase-promoting complex. Cells regulate anaphase entry by delaying securin ubiquitination until all chromosomes have attached to the mitotic spindle. Though no longer regulated by this mitotic surveillance mechanism, sister separation remains tightly cell cycle regulated in yeast mutants lacking securin. We show here that the Polo/Cdc5 kinase phosphorylates serine residues adjacent to Scc1 cleavage sites and strongly enhances their cleavage. Phosphorylation of **separase** recognition sites may be highly conserved and regulates sister chromatid separation independently of securin.

L7 ANSWER 6 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2000472355 MEDLINE
DOCUMENT NUMBER: 20428554 PubMed ID: 10970883

TITLE: Degradation of Drosophila PIM regulates sister chromatid separation during mitosis.
AUTHOR: Leismann O; Herzig A; Heidmann S; Lehner C F
CORPORATE SOURCE: Department of Genetics, University of Bayreuth, 95440 Bayreuth, Germany.
SOURCE: GENES AND DEVELOPMENT, **(2000 Sep 1)** 14 (17) 2192-205.
Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001003

AB Drosophila Pimples (PIM) and Three rows (THR) are required for sister chromatid separation in mitosis. PIM accumulates during interphase and is degraded rapidly during mitosis. This degradation is dependent on a destruction box similar to that of B-type cyclins. Nondegradable PIM with a mutant destruction box can rescue sister chromatid separation in pim mutants but only when expressed at low levels. Higher levels of nondegradable PIM, as well as overexpression of wild-type PIM, **inhibit** sister chromatid separation. Moreover, cells arrested in mitosis before sister chromatid separation (by colcemid or by mutations in fizzy/CDC20) fail to degrade PIM. Thus, although not related by primary sequence, PIM has intriguing functional similarities to the securin proteins of budding yeast, fission yeast, and vertebrates. Whereas these securins are known to form a complex with **separins**, we show that PIM associates in vivo with THR, which does not contain the conserved **separin** domain.

L7 ANSWER 7 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2000394766 MEDLINE
DOCUMENT NUMBER: 20312182 PubMed ID: 10855492
TITLE: Destruction of the securin Pds1p occurs at the onset of anaphase during both meiotic divisions in yeast.
AUTHOR: Salah S M; Nasmyth K
CORPORATE SOURCE: Vienna Biocenter, Institute of Biochemistry and Molecular Biology, Austria.
SOURCE: CHROMOSOMA, **(2000)** 109 (1-2) 27-34.
Journal code: 2985138R. ISSN: 0009-5915.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20030225
Entered Medline: 20000811

AB Sister chromatid cohesion is established during DNA replication and depends on a multiprotein complex called cohesin. At the onset of anaphase the cohesive structures that hold sisters together must be destroyed to allow segregation of sisters. In the budding yeast Saccharomyces cerevisiae loss of sister chromatid cohesion depends on a separating protein (**separin**) called Esp1. At the metaphase to anaphase transition, **separin** is activated by proteolysis of its **inhibitory** subunit (securin) called Pds1. This process is mediated by the anaphase promoting complex and an accessory protein Cdc20. In meiosis a single round of DNA replication is followed by two successive rounds of segregation. Thus loss of cohesion is spun out over two divisions. By studying the mechanisms that initiate anaphase in meiotic division we show that the yeast securin Pds1p is present in meiotic nuclei and is destroyed at the onset of each meiotic division. We also show that securin destruction depends on Cdc20p which accumulates within nuclei around the time of Pds1p's disappearance.

L7 ANSWER 8 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2000118102 MEDLINE

DOCUMENT NUMBER: 20118102 PubMed ID: 10651900
TITLE: Cell cycle mechanisms of sister chromatid separation; roles of Cut1/separin and Cut2/securin.
AUTHOR: Yanagida M
CORPORATE SOURCE: Department of Gene Mechanisms, Graduate School of Biostudies, Kyoto University, Kitashirakawa-Oiwakecho, Sakyo-ku, Kyoto 606-8502, Japan..
yanagida@kozo.biophys.kyotou.ac.jp
SOURCE: GENES TO CELLS, **(2000 Jan)** 5 (1) 1-8. Ref: 30
Journal code: 9607379. ISSN: 1356-9597.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20030225
Entered Medline: 20000424

AB The correct transmission of chromosomes from mother to daughter cells is fundamental for genetic inheritance. Separation and segregation of sister chromatids in growing cells occurs in the cell cycle stage called 'anaphase'. The basic process of sister chromatid separation is similar in all eukaryotes: many gene products required are conserved. In this review, the roles of two proteins essential for the onset of anaphase in fission yeast, Cut2/securin and Cut1/**separin**, are discussed with regard to cell cycle regulation, and compared with the postulated roles of homologous proteins in other organisms. Securin, like mitotic cyclins, is the target of the anaphase promoting complex (APC)/cyclosome and is polyubiquitinated before destruction in a manner dependent upon the destruction sequence. The anaphase never occurs properly in the absence of securin destruction. In human cells, securin is an oncogene. **Separin** is a large protein (MW approximately 180 kDa), the C-terminus of which is conserved, and is thought to be **inhibited** by association with securin at the nonconserved N-terminus. In the budding yeast, Esp1/**separin** is thought to be a component of proteolysis against Scc1, an essential subunit of cohesin which is thought to link duplicated sister chromatids up to the anaphase. Whether fission yeast Cut1/**separin** is also implicated in proteolysis of cohesin is discussed.

L7 ANSWER 9 OF 10 MEDLINE on STN
ACCESSION NUMBER: 1999221850 MEDLINE
DOCUMENT NUMBER: 99221850 PubMed ID: 10203756
TITLE: Separating sister chromatids.
AUTHOR: Nasmyth K
CORPORATE SOURCE: IMP Research Institute of Molecular Pathology, Dr. Bohr-Gasse 7, A-1030 Vienna, Austria..
Nasmyth@nt.imp.univie.ac.at
SOURCE: TRENDS IN BIOCHEMICAL SCIENCES, **(1999 Mar)** 24 (3) 98-104. Ref: 68
Journal code: 7610674. ISSN: 0968-0004.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 20020420
Entered Medline: 19990609

AB Loss of cohesion between sister chromatids triggers their segregation during anaphase. Recent work has identified both a cohesin complex that holds sisters together and a sister-separating protein, **separin**, that destroys cohesion. **Separins** are bound by **inhibitory** proteins whose proteolysis at the metaphase-anaphase transition is mediated by the anaphase-promoting complex and its activator

protein CDC20 (APCCDC20). When chromosomes are misaligned, a surveillance mechanism (checkpoint) blocks sister separation by **inhibiting** APCCDC20. Defects in this apparatus are implicated in causing aneuploidy in human cells.

L7 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER:	2002:158292 BIOSIS
DOCUMENT NUMBER:	PREV200200158292
TITLE:	Regulation of anaphase by phosphorylation.
AUTHOR(S):	Stemmann, Olaf (1); Zou, Hui (1); Gygi, Steven (1); Kirschner, Marc W. (1)
CORPORATE SOURCE:	(1) Cell Biology, Harvard Medical School, 240 Longwood Ave., Boston, MA, 02115 USA
SOURCE:	Molecular Biology of the Cell, (**Nov, 2001**) Vol. 12, No. Supplement, pp. 408a. http://www.molbiolcell.org/. print. Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology Washington DC, USA December 08-12, 2001 ISSN: 1059-1524.
DOCUMENT TYPE:	Conference
LANGUAGE:	English

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=> s separase/cn
L1            1 SEPARASE/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   351527-77-0  REGISTRY
CN   Separin (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Proteinase Esp1
CN   Separase
CN   Sister-sepg. protease separin
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
              39 REFERENCES IN FILE CA (1907 TO DATE)
              40 REFERENCES IN FILE CAPLUS (1907 TO DATE)
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=> d his

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     INDEX 'CAOLD, CAPLUS, CASREACT, CROPU, DGENE, DPCI, ENCOMPPAT2,
     EUROPATFULL, FSTA, IFIPAT, INPADOC, JAPIO, NTIS, PAPERCHEM2, PATDD,
     PATDPA, PATDPAFULL, PATOSDE, PATOSEP, PATOSWO, PCTFULL, PCTGEN, PIRA,
     RAPRA, RDISCLOSURE, SYNTHLINE, TULSA, TULSA2, USPATFULL, ...' ENTERED AT
     13:28:52 ON 15 OCT 2003
                SEA SEPARASE
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              43   FILE CAPLUS
               3   FILE EUROPATFULL
               2   FILE IFIPAT
               4   FILE INPADOC
               2   FILE NTIS
               2   FILE PATDPAFULL
               1   FILE PATOSEP
               2   FILE PATOSWO
              10   FILE PCTFULL
               6   FILE USPATFULL
               2   FILE WPIDS
               2   FILE WPINDEX
L1             QUE SEPARASE
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     PATDPAFULL, PATOSWO, WPIDS, PATOSEP' ENTERED AT 13:29:09 ON 15 OCT 2003
L2            77 S SEPARASE
L3            42 S L2 (L) INHIBIT?
L4            32 S L3 (L) (ASSA? OR SUBSTRAT? OR PROTEIN OR PEPTIDE)
L5            23 DUP REM L4 (9 DUPLICATES REMOVED)
L6             4 S L5 AND PY<=2001
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=> d ibib ab 1-4

L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:11853 CAPLUS
DOCUMENT NUMBER: 136:162818
TITLE: Dual inhibition of sister chromatid separation at metaphase
AUTHOR(S): Stemmann, Olaf; Zou, Hui; Gerber, Scott A.; Gygi, Steven P.; Kirschner, Marc W.
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cell (Cambridge, MA, United States) (**2001**), 107(6), 715-726
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sepn. of sister chromatids in anaphase is mediated by separase, an endopeptidase that cleaves the chromosomal cohesin SCC1. Separase is inhibited by securin, which is degraded at the metaphase-anaphase transition. Using Xenopus egg exts., we demonstrate that high CDC2 activity inhibits anaphase but not securin degrdn. We show that separase is kept inactive under these conditions by a mechanism independent of binding to securin. Mutation of a single phosphorylation site on separase relieves the inhibition and rescues chromatid sepn. in exts. with high CDC2 activity. Using quant. mass spectrometry, we show that, in intact cells, there is complete phosphorylation of this site in metaphase and significant dephosphorylation in anaphase. We propose that separase activation at the metaphase-anaphase transition requires the removal of both securin and an inhibitory phosphate.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:786622 CAPLUS
DOCUMENT NUMBER: 136:98960
TITLE: Phosphorylation of the cohesin subunit Scc1 by Polo/Cdc5 kinase regulates sister chromatid separation in yeast
AUTHOR(S): Alexandru, Gabriela; Uhlmann, Frank; Mechtler, Karl; Poupart, Marc-Andre; Nasmyth, Kim
CORPORATE SOURCE: Res. Inst. of Mol. Pathol. (IMP), Vienna, A-1030, Austria
SOURCE: Cell (Cambridge, MA, United States) (**2001**), 105(4), 459-472
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB At the onset of anaphase, a caspase-related protease (**separase**) destroys the link between sister chromatids by cleaving the cohesin subunit Scc1. During most of the cell cycle, **separase** is kept inactive by binding to an **inhibitory protein** called securin. **Separase** activation requires proteolysis of securin, which is mediated by a ubiquitin **protein** ligase called the anaphase-promoting complex. Cells regulate anaphase entry by delaying securin ubiquitination until all chromosomes have attached to the mitotic spindle. Though no longer regulated by this mitotic surveillance mechanism, sister sepn. remains tightly cell cycle regulated in yeast mutants lacking securin. We show here that the Polo/Cdc5 kinase phosphorylates serine residues adjacent to Scc1 cleavage sites and strongly enhances their cleavage. Phosphorylation of **separase** recognition sites may be highly conserved and regulates sister chromatid sepn. independently of securin.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:756258 CAPLUS

DOCUMENT NUMBER: 136:306549
TITLE: Role of the kinetochore protein Ndc10 in mitotic checkpoint activation in Saccharomyces cerevisiae
AUTHOR(S): Fraschini, R.; Beretta, A.; Lucchini, G.; Piatti, S.
CORPORATE SOURCE: Dipartimento di Biotecnologie e Bioscienze, Universita degli Studi di Milano-Bicocca, Milan, 20126, Italy
SOURCE: Molecular Genetics and Genomics (**2001**), 266(1), 115-125
CODEN: MGGOAA; ISSN: 1617-4615
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mitotic checkpoints delay cell cycle progression in response to alterations in the mitotic app., thus ensuring correct chromosome segregation. While improper spindle orientation activates the Bub2/Bfa1-dependent checkpoint in budding yeast, delaying exit from mitosis, lack of bipolar kinetochore-microtubule attachment activates a signal transduction cascade that prevents both anaphase onset and exit from mitosis by **inhibiting** the Cdc20/APC (Anaphase Promoting Complex)-mediated proteolysis of securin and inactivation of mitotic cyclin-dependent kinases (CDKs), resp. Proteolysis of the securin Pds1 is necessary to liberate the **separase** Esp1, which then triggers sister chromatid sepn., whereas inactivation of mitotic CDKs is a prerequisite for exit from mitosis and for starting a new round of DNA replication in the next cell cycle. In budding yeast, this latter checkpoint response involves the **proteins** Mad1, 2, 3, Bub1 and Bub3, whose vertebrate counterparts localize to unattached kinetochores. Mutations that alter other kinetochore **proteins** result in mitotic checkpoint activation, while the ndc10-1 mutation not only impairs kinetochore function, but also disrupts the checkpoint response, indicating a role for Ndc10 in this process. Here the authors present evidence that Ndc10 is not part of the Bub2/Bfa1-dependent pathway, and its role in the checkpoint response might also be different from that of the other Mad and Bub **proteins**. Indeed, Ndc10, unlike other mitotic checkpoint **proteins**, is not required for the mitotic block induced by over-expression of the Mps1 **protein** kinase, which is implicated in mitotic checkpoint control. Furthermore, the delay in mitotic exit caused by non-degradable Pds1, which does not require Mad and Bub **proteins**, depends on Ndc10 function. The authors propose that a pathway involving Ndc10 might monitor defects in the mitotic app. independently of the Mad and Bub **proteins**. Since the Esp1 **separase** is required for exit from mitosis in both ndc10-1 and nocodazole-treated mad2.DELTA. cells, the two signal transduction cascades might ultimately converge on the inactivation of Esp1.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:749385 CAPLUS
DOCUMENT NUMBER: 136:321097
TITLE: Drosophila separase is required for sister chromatid separation and binds to PIM and THR
AUTHOR(S): Jager, Hubert; Herzig, Alf; Lehner, Christian F.; Heidmann, Stefan
CORPORATE SOURCE: Department of Genetics, University of Bayreuth, Bayreuth, 95440, Germany
SOURCE: Genes & Development (**2001**), 15(19), 2572-2584
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Drosophila PIM and THR are required for sister chromatid sepn. in mitosis and assoc. in vivo. Neither of these two **proteins** shares significant sequence similarity with known **proteins**. However, PIM has functional similarities with securin **proteins**. Like securin, PIM is degraded at the metaphase-to-anaphase transition and this degrdn. is required for sister chromatid sepn. Securin binds and

inhibits separase, a conserved cysteine endoprotease. Proteolysis of securin at the metaphase-to-anaphase transition activates **separase**, which degrades a conserved cohesin subunit, thereby allowing sister chromatid sepn. To address whether PIM regulates **separase** activity or functions with THR in a distinct pathway, we have characterized a Drosophila **separase** homolog (SSE). SSE is an unusual member of the **separase** family. SSE is only about one-third the size of other **separases** and has a diverged endoprotease domain. However, our genetic analyses show that SSE is essential and required for sister chromatid sepn. during mitosis. Moreover, we show that SSE assocs. with both PIM and THR. Although our work shows that **separase** is required for sister chromatid sepn. in higher eukaryotes, in addn., it also indicates that the regulatory **proteins** have diverged to a surprising degree, particularly in Drosophila.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ab 1-23

L5 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:491423 CAPLUS
DOCUMENT NUMBER: 139:65403
TITLE: Human cDNAs encoding separase, methods for modulation of separase activity in sister chromatid DNA separation, and uses thereof
INVENTOR(S): Kirschner, Marc W.; Stemmann, Olaf; Zou, Hui; Gygi, Steven P.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003052120	A2	20030626	WO 2002-US40085	20021216
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003148462	A1	20030807	US 2002-320175	20021216

PRIORITY APPLN. INFO.: US 2001-340682P P 20011214

AB The invention provides nucleic acid mols., designated **separase** nucleic acid mols., which encode **separase**, an endopeptidase that modulates sister chromatid sepn. The invention also provides recombinant expression vectors contg. **separase** nucleic acid mols. and host cells into which the expression vectors have been introduced. The invention still further provides **separase proteins**, fusion **proteins**, antigenic **peptides** and anti-**separase** antibodies. The invention also provides methods for the identification of modulators of **separase**, methods of modulating **separase**, methods of modulating sister chromatid sepn. at metaphase, and methods for the treatment of disorders related to aberrant sister chromatid sepn., such as cancer, Down's syndrome, and spontaneous fetal abortion. Sister chromatid cohesion is mediated by a multiprotein complex, cohesin. At the metaphase to anaphase transition in vertebrates, cohesin complexes in centromeric regions are removed by cleavage of the cohesin subunit SCC1 by a cysteine endopeptidase, **separase**. Before anaphase, **separase** is **inhibited** by assocn. with the **inhibitor** securin and by CDC2/cyclinB1-mediated phosphorylation of **separase**. Human **separase** cDNA contg. a putative unspliced intron was cloned and an expression vector was developed for an in vitro **separase** activity **assay**. In cell exts. with high CDC2 activity, **separase** was inactive even in the absence of securin and some cleavage,, possibly self-cleavage, of **separase** was obsd. Phosphopeptide mapping and site-directed mutagenesis demonstrated that **inhibitory** phosphorylation of **separase** is due to phosphorylation at serine residue 1126 and threonine residue 1346. Phosphorylation site mutants rescued sister chromatid sepn. and cohesin cleavage in a cell ext. with high CDC2 activity.

L5 ANSWER 2 OF 23 USPATFULL on STN DUPLICATE 2
ACCESSION NUMBER: 2003:213824 USPATFULL
TITLE: Dual inhibition of sister chromatid separation at metaphase
INVENTOR(S): Kirschner, Marc W., Newton, MA, UNITED STATES
Stemmann, Olaf, Munich, GERMANY, FEDERAL REPUBLIC OF

Zou, Hui, Dallas, TX, UNITED STATES
Gygi, Steven P., Foxborough, MA, UNITED STATES
PATENT ASSIGNEE(S): President and fellows of Harvard College, Cambridge, MA, UNITED STATES, 02138 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003148462	A1	20030807
APPLICATION INFO.:	US 2002-320175	A1	20021216 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-340682P	20011214 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BANNER & WITCOFF, LTD., 28 STATE STREET, 28th FLOOR, BOSTON, MA, 02109-9601
NUMBER OF CLAIMS: 78
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Page(s)
LINE COUNT: 2926
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides nucleic acid molecules, designated separase nucleic acid molecules, which encode separase, an endopeptidase that modulates sister chromatid separation. The invention also provides recombinant expression vectors containing separase nucleic acid molecules and host cells into which the expression vectors have been introduced. The invention still further provides separase proteins, fusion proteins, antigenic peptides and anti-separase antibodies. The invention also provides methods for the identification of modulators of separase, methods of modulating separase, methods of modulating sister chromatid separation, and methods for the treatment of disorders related to aberrant sister chromatid separation, such as cancer, Down's syndrome, and spontaneous fetal abortion.

L5 ANSWER 3 OF 23 PCTFULL COPYRIGHT 2003 Univentio on STN
ACCESSION NUMBER: 2003016335 PCTFULL ED 20030313 EW 200309
TITLE (ENGLISH): IRREVERSIBLE CYSTEINE PROTEASE **INHIBITORS** OF LEGUMAIN
TITLE (FRENCH): **INHIBITEURS** IRREVERSIBLES DE LA CYSTEINE PROTEASE DE LA LEGUMAINE
INVENTOR(S): NIESTROJ, Andre, Grosse Brunnenstrasse 31, 06114 Halle/Saale, DE [DE, DE];
HEISER, Ulrich, Franz-Schubert-Strasse 5, 06108 Halle/Saale, DE [DE, DE];
GERHARTZ, Bernd, Haaner Weg 34, 06246 Bad Lauchstaedt, DE [DE, DE];
HOFFMANN, Matthias, Froebelstrasse 1d, 06688 Wengelsdorf, DE [DE, DE];
DEMUTH, Hans-Ulrich, Hegelstrasse 14, 06114 Halle/Saale, DE [DE, DE]
PATENT ASSIGNEE(S): PROBIODRUG AG, Weinbergweg 22, 06120 Halle/Saale, DE [DE, DE], for all designates States except US;
NIESTROJ, Andre, Grosse Brunnenstrasse 31, 06114 Halle/Saale, DE [DE, DE], for US only;
HEISER, Ulrich, Franz-Schubert-Strasse 5, 06108 Halle/Saale, DE [DE, DE], for US only;
GERHARTZ, Bernd, Haaner Weg 34, 06246 Bad Lauchstaedt, DE [DE, DE], for US only;
HOFFMANN, Matthias, Froebelstrasse 1d, 06688 Wengelsdorf, DE [DE, DE], for US only;
DEMUTH, Hans-Ulrich, Hegelstrasse 14, 06114 Halle/Saale, DE [DE, DE], for US only
AGENT: FORSTMEYER, Dietmar$, Boeters & Bauer, Bereiteranger 15, 81541 Muenchen$, DE
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2003016335	A2	20030227

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-EP8202 A 20020723
PRIORITY INFO.: US 2001-60/311,790 20010813

ABEN Presented are compounds represented by the following general formulas (I) and (II), for **inhibiting** cysteine protease legumain for modulating associated disease states in subjects.

ABFR L'invention se rapporte a des composes representes par les formules (I) et (II), et utilises dans l'**inhibition** de la cysteine protease de la legumaine afin de moduler les etats pathologiques associes chez des sujets.

L5 ANSWER 4 OF 23 USPATFULL on STN
ACCESSION NUMBER: 2003:120777 USPATFULL
TITLE: Class of 12mer peptides that inhibit the function of the mitotic check point protein Mad2
INVENTOR(S): Yu, Hongtao, Dallas, TX, UNITED STATES
Tang, Zhanyun, Dallas, TX, UNITED STATES
Luo, Xuelian, Dallas, TX, UNITED STATES
Rizo-Rey, Jose, Dallas, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003083261	A1	20030501
APPLICATION INFO.:	US 2001-845612	A1	20010430 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Steven L. Highlander, Fulbright & Jaworski L.L.P., Suite 2400, 600 Congress Avenue, Austin, TX, 78701
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 3442
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods of inhibiting Mad2 function by using a peptide that binds to Mad2, designated Mad2 binding peptides (MBPs). More particularly, the Mad2 binding peptides may be used to inhibit cancer cell proliferation. Yet further, Mad2 binding peptides may be used in combination with a second cancer therapy, for example taxol.

L5 ANSWER 5 OF 23 EUROPATFULL COPYRIGHT 2003 WILA on STN

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1321529 EUROPATFULL EW 200326 FS OS
TITLE: Methods for identifying compounds that modulate sister chromatid cohesion.
Verfahren zum Nachweis von Modulatoren von Schwesterchromatid Kohaesion.
Procede d'identification des modulateurs de la cohesion des chromatides soeurs.
INVENTOR(S): Eisenhaber, Frank, Kefedergrundgasse 5/D7, A-1210 Wien, AT;
Schleiffer, Alexander, Pasettistrasse 75/1/10, A-1200 Wien, AT;
Ivanov, Dimitri, Pernerstorfer Gasse 66/9, A-1100 Wien,

AT;
Nasmyth, Kim, Sonnenfelsgasse 5,, A-1010 Wien, AT
PATENT ASSIGNEE(S): BOEHRINGER INGELHEIM INTERNATIONAL GmbH, Postfach 200, 55218 Ingelheim am Rhein, DE
PATENT ASSIGNEE NO: 291803
AGENT: Laudien, Dieter, Dr. et al., Boehringer Ingelheim GmbH Abteilung Patente, Postfach 200, 55216 Ingelheim, DE
AGENT NUMBER: 48064
OTHER SOURCE: MEPA2003049 EP 1321529 A1 0015
SOURCE: Wila-EPZ-2003-H26-T1a
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R TR; R AL; R LT; R LV; R MK; R RO; R SI
PATENT INFO.PUB.TYPE: EPA1 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 1321529	A1	20030625

'OFFENLEGUNGS' DATE: 20030625
APPLICATION INFO.: EP 2001-130640 20011221
ABEN Method for identifying compounds which modulates cohesion of sister chromatids by modulating the acetyltransferase activity of Eco1 <image>

L5 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:216535 CAPLUS
DOCUMENT NUMBER: 139:20129
TITLE: A non-proteolytic function of separase links the onset of anaphase to mitotic exit
AUTHOR(S): Sullivan, Matt; Uhlmann, Frank
CORPORATE SOURCE: Cancer Research UK, Lincoln's Inn Fields Laboratories, Chromosome Segregation Laboratory, London, WC2A 3PX, UK
SOURCE: Nature Cell Biology (2003), 5(3), 249-254
CODEN: NCBIFN; ISSN: 1465-7392
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Separase** is a protease that triggers chromosome segregation at anaphase onset by cleaving cohesin, the chromosomal **protein** complex responsible for sister chromatid cohesion. After anaphase, cells exit from mitosis; i.e., they complete downregulation of cyclin-dependent kinase activity, undergo cytokinesis and enter G1 of the next cell cycle. Here we show that **separase** activation at the onset of anaphase is sufficient to promote release from the nucleolus and activation of the budding yeast phosphatase, Cdc14, a key step in mitotic exit. The ability of **separase** to activate Cdc14 is independent of its protease function but may involve promoting phosphorylation of the Cdc14 **inhibitor** Net1. This novel **separase** function is coregulated with its proteolytic activity by the **separase inhibitor** securin. This helps to explain the coupling of anaphase and mitotic exit - after securin degrdn. at anaphase onset, **separase** cleaves cohesin to trigger chromosome segregation and concurrently uses a non-proteolytic mechanism to initiate mitotic exit.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:144425 CAPLUS
DOCUMENT NUMBER: 139:32377
TITLE: Western blot screening for monoclonal antibodies against human separase
AUTHOR(S): Chestukhin, Anton; DeCaprio, James A.
CORPORATE SOURCE: Dana-Farber Cancer Institute, Department of Medical Oncology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Immunological Methods (2003), 274(1-2),

105-113
CODEN: JIMMBG; ISSN: 0022-1759
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Separase** is a cysteine protease that participates in sepn. of sister chromatids during mitosis. Human **separase** is a 230-kDa enzyme that is **inhibited** by binding to its **protein inhibitor** securin, specific phosphorylation, and subcellular localization. To further characterize human **separase**, we raised monoclonal antibodies specific against a C-terminal fragment of the **protein**. A crit. step in monoclonal antibody prodn. procedure is the primary screening of hybridoma supernatants. Here we report primary screening protocol utilizing Western blot anal. The described screening protocol is carried out using fusion of a human **separase** fragment with two different purifn. tags, maltose-binding **protein** (MBP) and glutathione S-transferase (GST). Immunization by MBP-fusion was followed by primary screening with both MBP- and GST-**separase** fusions combined in the same prepn. sepd. in SDS-PAGE. This highly sensitive screening approach reduced the no. of pos. signals by eliminating antibodies specific for the purifn. tag used in the immunization procedure. The described **separase**-specific antibodies were suitable for detection of endogenous **separase** in crude exts., immunopptn., and immunofluorescent cell staining expts. The presented procedure is fast, reproducible and could be adopted as a primary screening scheme for a variety of **protein** antigens.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 23 PCTFULL COPYRIGHT 2003 Univentio on STN DUPLICATE 3
ACCESSION NUMBER: 2002057566 PCTFULL ED 20020801 EW 200230
TITLE (ENGLISH): METHOD FOR IDENTIFYING COMPOUNDS MODULATING SISTER CHROMATID SEPARATION
TITLE (FRENCH): PROCEDE RELATIF A L'IDENTIFICATION DE COMPOSES MODULANT LA SEPARATION DES CHROMATIDES JUMEAUX
INVENTOR(S): PETERS, Jan-Michael, Kielmannseggasse 14, A-2100 Korneuburg, AT [DE, AT];
WAIZENEGGER, Irene, Lechnerstrasse 13/18, A-1030 Wien, AT [DE, AT];
SOMMERGRUBER, Wolfgang, Linzer-Strasse 19/Haus 4, A-3002 Purkersdorf, AT [AT, AT]
PATENT ASSIGNEE(S): BOEHRINGER INGELHEIM INTERNATIONAL GMBH, Postfach 200, 55216 Ingelheim am Rhein, DE [DE, DE], for all designates States except US;
PETERS, Jan-Michael, Kielmannseggasse 14, A-2100 Korneuburg, AT [DE, AT], for US only;
WAIZENEGGER, Irene, Lechnerstrasse 13/18, A-1030 Wien, AT [DE, AT], for US only;
SOMMERGRUBER, Wolfgang, Linzer-Strasse 19/Haus 4, A-3002 Purkersdorf, AT [AT, AT], for US only
AGENT: LAUDIEN, Dieter$, Boehringer Ingelheim GmbH, 55216 Ingelheim am Rhein$, DE
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002057566	A2	20020725

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-EP529 A 20020119
PRIORITY INFO.: EP 2001-01101252.3 20010119
ABEN Screening methods for identifying **separase inhibitors** based on active forms of **separase** and compounds identified in such methods.
ABFR L'invention concerne des procedes de criblage qui assurent l'identification d'**inhibiteurs** de **separase**, compte tenu des formes actives de **separase**. L'invention concerne egalement des composes identifies par le biais de ces procedes.

L5 ANSWER 9 OF 23 USPATFULL on STN DUPLICATE 4
ACCESSION NUMBER: 2002:294577 USPATFULL
TITLE: Method for identifying compounds modulating sister chromatid separation
INVENTOR(S): Peters, Jan-Michael, Korneuburg, AUSTRIA
Waizenegger, Irene, Vienna, AUSTRIA
Sommergruber, Wolfgang, Purkersdorf, AUSTRIA
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164620	A1	20021107
APPLICATION INFO.:	US 2002-51311	A1	20020122 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2001-101252	20010119
	US 2001-297440P	20010613 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STERNE, KESSLER, GOLDSTEIN & FOX PLLC, 1100 NEW YORK AVENUE, N.W., SUITE 600, WASHINGTON, DC, 20005-3934
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 1019
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Screening methods for identifying separase inhibitors based on active forms of separase and compounds identified in such methods.

L5 ANSWER 10 OF 23 EUROPATFULL COPYRIGHT 2003 WILA on STN DUPLICATE 5

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1227160 EUROPATFULL EW 200231 FS OS
TITLE: Compounds modulating sister chromatid separation and method for identifying same.
Verbindungen, die die Trennung von Schwesterchromatiden modulieren, und Verfahren fuer das Identifizieren dieser Verbindungen.
Des composes qui influent la separation des chromatides soeurs ainsi qu'une methode pour les identifier.
INVENTOR(S): Peters, Jan-Michael, Dr., Kielmannseggasse 14, 2100 Korneuburg, AT;
Waizenegger, Irene, Lechnergasse 13/18, 1030 Wien, AT
PATENT ASSIGNEE(S): BOEHRINGER INGELHEIM INTERNATIONAL GmbH, Postfach 200, 55218 Ingelheim am Rhein, DE
PATENT ASSIGNEE NO: 291803
AGENT: Laudien, Dieter, Dr. et al., Boehringer Ingelheim International GmbH ZA Patente Postfach 200, 55216 Ingelheim am Rhein, DE
AGENT NUMBER: 48061
OTHER SOURCE: BEPA2002064 EP 1227160 A1 0019
SOURCE: Wila-EPZ-2002-H31-T1a
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R

GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R TR; R AL; R LT; R LV; R MK; R RO; R SI
PATENT INFO.PUB.TYPE: EPA1 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 1227160	A1	20020731

'OFFENLEGUNGS' DATE: 20020731
APPLICATION INFO.: EP 2001-101252 20010119
ABEN Screening methods for identifying **separase inhibitors** based on active forms of **separase** and compounds identified in such methods <image>

L5 ANSWER 11 OF 23 PCTFULL COPYRIGHT 2003 Univentio on STN
ACCESSION NUMBER: 2002076383 PCTFULL ED 20021011 EW 200240
TITLE (ENGLISH): SECURIN IS REQUIRED FOR CHROMOSOMAL STABILITY IN HUMAN CELLS
TITLE (FRENCH): PRESENCE NECESSAIRE DE LA SECURINE POUR LA STABILITE CHROMOSOMIQUE DANS LES CELLULES HUMAINES
INVENTOR(S): VOGELSTEIN, Bert, 3700 Breton Way, Baltimore, MD 21208, US [US, US];
KINZLER, Kenneth, W., 1403 Halkirk Way, BelAir, MD 21209, US [US, US];
JALLEPALLI, Prasad, Apartment 101, 2005 Fitzwarren Place, Baltimore, MD 21209, US [US, US];
LENGAUER, Christoph, 9212 Adalee Court, Columbia, MD 21045, US [AU, US]
PATENT ASSIGNEE(S): THE JOHNS HOPKINS UNIVERSITY, Suite 906, 111 Market Place, Baltimore, MD 21202, US [US, US], for all designates States except US;
VOGELSTEIN, Bert, 3700 Breton Way, Baltimore, MD 21208, US [US, US], for US only;
KINZLER, Kenneth, W., 1403 Halkirk Way, BelAir, MD 21209, US [US, US], for US only;
JALLEPALLI, Prasad, Apartment 101, 2005 Fitzwarren Place, Baltimore, MD 21209, US [US, US], for US only;
LENGAUER, Christoph, 9212 Adalee Court, Columbia, MD 21045, US [AU, US], for US only
AGENT: KAGAN, Sarah, A.$, Banner & Witcoff, Ltd., 11th floor, 1001 G Street, N.W., Washington, DC 20001-4597$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002076383	A2	20021003

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-US6643 A 20020320
PRIORITY INFO.: US 2001-09/815,340 20010323
ABEN Securin-deficient cells and their securin-proficient counterparts are useful for screening potential anti-tumor agents. Potential therapeutic agents are screened for the ability to preferentially **inhibit** or kill a securin-deficient cell. The association of securin deficiency and chromosomal instability leading to aneuploidy, renders securin an excellent target for chemotherapeutic drug development.
ABFR Des cellules deficitaires en securine et leurs contreparties riches en securine sont utiles pour la recherche systematique d'agents

potentiellement antitumoraux. Le criblage d'agents therapeutiques potentiels porte sur leur aptitude a inhiber ou a tuer une cellule deficitaire en securine. L'association d'un deficit en securine et l'instabilite chromosomique conduisant a l'aneuploidie fait de la securine une cible remarquable pour la mise au point de medicaments chimiotherapeutiques.

L5 ANSWER 12 OF 23 USPATFULL on STN
ACCESSION NUMBER: 2002:251075 USPATFULL
TITLE: Securin is required for chromosomal stability in human cells
INVENTOR(S): Vogelstein, Bert, Baltimore, MD, UNITED STATES
Kinzler, Kenneth W., Bel Air, MD, UNITED STATES
Jallepalli, Prasad, Baltimore, MD, UNITED STATES
Lengauer, Christoph, Columbia, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002137018	A1	20020926
APPLICATION INFO.:	US 2001-815340	A1	20010323 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 875
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Securin-deficient cells and their isogenic securin-proficient counterparts are useful for screening potential anti-tumor agents. Potential therapeutic agents are screened for the ability to preferentially inhibit or kill a securin-deficient cell. The association of securin deficiency and chromosomal instability leading to aneuploidy, renders securin an excellent target for chemotherapeutic drug development.

L5 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:753616 CAPLUS
DOCUMENT NUMBER: 138:52965
TITLE: Proteolytic cleavage of the THR subunit during anaphase limits Drosophila separase function
AUTHOR(S): Herzig, Alf; Lehner, Christian F.; Heidmann, Stefan
CORPORATE SOURCE: Department of Genetics, University of Bayreuth, Bayreuth, 95440, Germany
SOURCE: Genes & Development (2002), 16(18), 2443-2454
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sister-chromatid sepn. in mitosis requires proteolytic cleavage of a cohesin subunit. **Separase**, the corresponding protease, is activated at the metaphase-to-anaphase transition. Activation involves proteolysis of an **inhibitory** subunit, securin, following ubiquitination mediated by the anaphase-promoting complex/cyclosome. In Drosophila, the securin PIM assocs. not only with **separase** (SSE), but also with an addnl. **protein**, THR. THR is cleaved after the metaphase-to-anaphase transition. THR cleavage only occurs in functional SSE complexes and in a region that matches the **separase** cleavage-site consensus. Mutations in this region abolish mitotic THR cleavage. These results indicate that THR is cleaved by SSE. Expression of noncleavable THR variants results in cold-sensitive maternal-effect lethality. This lethality can be suppressed by a redn. of catalytically active SSE levels, indicating that THR cleavage inactivates SSE complexes. THR cleavage is particularly important during the process of cellularization, which follows completion of the last syncytial mitosis of early embryogenesis, suggesting that Drosophila **separase** has other targets in addn. to cohesin subunits.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:982278 CAPLUS
DOCUMENT NUMBER: 138:249613
TITLE: The Cdc20 Homolog, FZY-1, and Its Interacting Protein, IFY-1, Are Required for Proper Chromosome Segregation in Caenorhabditis elegans
AUTHOR(S): Kitagawa, Risa; Law, Elaine; Tang, Lois; Rose, Ann M.
CORPORATE SOURCE: Department of Medical Genetics, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Current Biology (2002), 12(24), 2118-2123
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Accurate chromosome segregation is achieved by a series of highly regulated processes that culminate in the metaphase-to-anaphase transition of the cell cycle. In the budding yeast Saccharomyces cerevisiae, the degrdn. of the securin **protein** Pds1 reverses the binding and **inhibition** of the **separase protein** Esp1 . Esp1 cleaves Scc1. That cleavage promotes the dissocn. of the cohesin complex from the chromosomes and leads the sepn. of sister chromatids. Proteolysis of Pds1 is regulated by the anaphase-promoting complex (APC), a large multi-subunit E3 ubiquitin ligase whose activity is regulated by Cdc20/Fizzy . We have previously shown that the Caenorhabditis elegans genes mdf-1/MAD1 and mdf-2/MAD2 encode key members of the spindle checkpoint. Loss of function of either gene leads to an accumulation of somatic and heritable defects and ultimately results in death. Here we show that a missense mutation in fzy-1/CDC20/Fizzy suppresses mdf-1 lethality. We identified a FZY-1-interacting **protein**, IFY-1, a novel destruction-box **protein**. IFY-1 accumulates in one-cell-arrested emb-30/APC4 embryos and interacts with SEP-1, a C. elegans **separase**, suggesting that IFY-1 functions as a C. elegans securin.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:540563 CAPLUS
DOCUMENT NUMBER: 137:273944
TITLE: Spo13 regulates cohesin cleavage
AUTHOR(S): Lee, Brian H.; Amon, Angelika; Prinz, Susanne
CORPORATE SOURCE: Center for Cancer Research, Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: Genes & Development (2002), 16(13), 1672-1681
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A key aspect of meiotic chromosome segregation is that cohesin, the **protein** complex that holds sister chromatids together, dissocs. from chromosome arms during meiosis I and from centromeric regions during meiosis II. The budding yeast **protein** Spo13 plays a key role in preventing centromeric cohesin from being lost during meiosis I. We have detd. the mol. basis for the metaphase arrest obtained when SPO13 is overexpressed during the mitotic cell cycle. Overexpression of SPO13 **inhibits** anaphase onset by at least two mechanisms. First, Spo13 causes a transient delay in degrdn. of the anaphase **inhibitor** Pds1. Second, Spo13 **inhibits** cleavage of the cohesin subunit Scc1/Mcd1 or its meiosis-specific homolog, Rec8, by the **separase** Esp1. The finding that Spo13 did not prevent cleavage of another Esp1 **substrate**, Slk19, suggests that overexpression of SPO13 is sufficient to prevent cohesin cleavage by protecting specific **substrates** from **separase** activity.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:471266 CAPLUS
DOCUMENT NUMBER: 138:300300
TITLE: Phosphorylation of the mitotic regulator Pds1/securin by Cdc28 is required for efficient nuclear localization of Esp1/separase
AUTHOR(S): Agarwal, Ritu; Cohen-Fix, Orna
CORPORATE SOURCE: The Laboratory of Molecular and Cellular Biology, National Institutes of Health, NIDDK, Bethesda, MD, 20892, USA
SOURCE: Genes & Development (2002), 16(11), 1371-1382
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sister chromatid sepn. at the metaphase-to-anaphase transition is induced by the proteolytic cleavage of one of the cohesin complex subunits. This process is mediated by a conserved protease called **separase**. **Separase** is assocd. with its **inhibitor**, securin, until the time of anaphase initiation, when securin is degraded in an anaphase-promoting complex/cyclosome (APC/C)-dependent manner. In budding yeast securin/Pds1 not only **inhibits separase**/Esp1, but also promotes its nuclear localization. The mol. mechanism and regulation of this nuclear targeting are presently unknown. Here we show that Pds1 is a **substrate** of the cyclin-dependent kinase Cdc28. Phosphorylation of Pds1 by Cdc28 is important for efficient binding of Pds1 to Esp1 and for promoting the nuclear localization of Esp1. Our results uncover a previously unknown mechanism for regulating the Pds1-Esp1 interaction and shed light on a novel role for Cdc28 in promoting the metaphase-to-anaphase transition in budding yeast.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:644214 CAPLUS
DOCUMENT NUMBER: 137:348269
TITLE: Regulation of human separase by securin binding and autocleavage
AUTHOR(S): Waizenegger, Irene C.; Gimenez-Abian, Juan F.; Wernic, Dominik; Peters, Jan-Michael
CORPORATE SOURCE: Research Institute of Molecular Pathology, Vienna, 1030, Austria
SOURCE: Current Biology (2002), 12(16), 1368-1378
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Sister chromatid sepn. is initiated by **separase**, a protease that cleaves cohesin and thereby dissolves sister chromatid cohesion. **Separase** is activated by the degrdn. of its **inhibitor** securin and by the removal of **inhibitory** phosphates. In human cells, **separase** activation also coincides with the cleavage of **separase**, but it is not known if this reaction activates **separase**, which protease cleaves **separase**, and how **separase** cleavage is regulated. Results: **Inhibition** of **separase** expression in human cells by RNA interference causes the formation of polyploid cells with large lobed nuclei. In mitosis, many of these cells contain abnormal chromosome plates with unsepd. sister chromatids. **Inhibitor** binding expts. in vitro reveal that securin prevents the access of **substrate** analogs to the active site of **separase**. Upon securin degrdn., the active site of full-length **separase** becomes accessible, allowing rapid autocatalytic cleavage of **separase** at one of three sites. The resulting N- and C-terminal fragments remain assocd. and can be reinhibited by securin. Conclusions: Our results suggest that **separase** is required for sister chromatid sepn. during mitosis in human cells. Our data further indicate that securin **inhibits separase** by blocking the access of **substrates** to the active site of **separase**. Securin

proteolysis allows autocatalytic processing of **separase** into a cleaved form, but **separase** cleavage is not essential for **separase** activation.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:548056 CAPLUS
DOCUMENT NUMBER: 137:243836
TITLE: The Dual Mechanism of Separase Regulation by Securin
AUTHOR(S): Hornig, Nadine C. D.; Knowles, Philip P.; McDonald, Neil Q.; Uhlmann, Frank
CORPORATE SOURCE: Chromosome Segregation Laboratory, Cancer Research UK, London Research Institute, London, WC2A 3PX, UK
SOURCE: Current Biology (2002), 12(12), 973-982
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Sister chromatid sepn. and segregation at anaphase onset are triggered by cleavage of the chromosomal cohesin complex by the protease **separase**. **Separase** is regulated by its binding partner securin in two ways: securin is required to support **separase** activity in anaphase; and, at the same time, securin must be destroyed via ubiquitylation before **separase** becomes active. The mol. mechanisms underlying this dual regulation of **separase** by securin are unknown. Results: We show that, in budding yeast, securin supports **separase** localization. **Separase** enters the nucleus independently of securin, but securin is required and sufficient to cause accumulation of **separase** in the nucleus, where its known cleavage targets reside. Securin also ensures that **separase** gains full proteolytic activity in anaphase. We also show that securin, while present, directly **inhibits** the proteolytic activity of **separase**. Securin prevents the binding of **separase** to its **substrates**. It also hinders the **separase** N terminus from interacting with and possibly inducing an activating conformational change at the protease active site 150 kDa downstream at the **protein**'s C terminus. Conclusions: Securin **inhibits** the proteolytic activity of **separase** in a 2-fold manner. While **inhibiting separase**, securin is able to promote nuclear accumulation of **separase** and help **separase** to become fully activated after securin's own destruction at anaphase onset.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:109232 CAPLUS
DOCUMENT NUMBER: 136:291515
TITLE: Separase, polo kinase, the kinetochore protein Slk19, and Spo12 function in a network that controls Cdc14 localization during early anaphase
AUTHOR(S): Stegmeier, Frank; Visintin, Rosella; Amon, Angelika
CORPORATE SOURCE: Center for Cancer Research Howard Hughes Medical Institute, Massachusetts Institute of Technology, E17-233, Cambridge, MA, 02139, USA
SOURCE: Cell (Cambridge, MA, United States) (2002), 108(2), 207-220
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In budding yeast, the phosphatase Cdc14, a key regulator of exit from mitosis, is released from its **inhibitor** Cfi1/Net1 in the nucleolus during anaphase. A signaling cascade, known as the mitotic exit network (MEN), controls this release. We have identified a regulatory network, the FEAR (Cdc fourteen early anaphase release) network that promotes Cdc14 release from the nucleolus during early anaphase. The FEAR network is comprised of the polo kinase Cdc5, the **separase** Esp1, the kinetochore-assocd. **protein** Slk19, and Spo12. We also show

that the FEAR network initiates Cdc14 release from Cfi1/Net1 during early anaphase, and MEN maintains Cdc14 in the released state during late anaphase. We propose that one function of Cdc14 released by the FEAR network is to stimulate MEN activity. cdc15.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:749385 CAPLUS
DOCUMENT NUMBER: 136:321097
TITLE: Drosophila separase is required for sister chromatid separation and binds to PIM and THR
AUTHOR(S): Jager, Hubert; Herzig, Alf; Lehner, Christian F.; Heidmann, Stefan
CORPORATE SOURCE: Department of Genetics, University of Bayreuth, Bayreuth, 95440, Germany
SOURCE: Genes & Development (2001), 15(19), 2572-2584
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Drosophila PIM and THR are required for sister chromatid sepn. in mitosis and assoc. in vivo. Neither of these two **proteins** shares significant sequence similarity with known **proteins**. However, PIM has functional similarities with securin **proteins**. Like securin, PIM is degraded at the metaphase-to-anaphase transition and this degrdn. is required for sister chromatid sepn. Securin binds and **inhibits separase**, a conserved cysteine endoprotease. Proteolysis of securin at the metaphase-to-anaphase transition activates **separase**, which degrades a conserved cohesin subunit, thereby allowing sister chromatid sepn. To address whether PIM regulates **separase** activity or functions with THR in a distinct pathway, we have characterized a Drosophila **separase** homolog (SSE). SSE is an unusual member of the **separase** family. SSE is only about one-third the size of other **separases** and has a diverged endoprotease domain. However, our genetic analyses show that SSE is essential and required for sister chromatid sepn. during mitosis. Moreover, we show that SSE assocs. with both PIM and THR. Although our work shows that **separase** is required for sister chromatid sepn. in higher eukaryotes, in addn., it also indicates that the regulatory **proteins** have diverged to a surprising degree, particularly in Drosophila.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:11853 CAPLUS
DOCUMENT NUMBER: 136:162818
TITLE: Dual inhibition of sister chromatid separation at metaphase
AUTHOR(S): Stemmann, Olaf; Zou, Hui; Gerber, Scott A.; Gygi, Steven P.; Kirschner, Marc W.
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cell (Cambridge, MA, United States) (2001), 107(6), 715-726
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sepn. of sister chromatids in anaphase is mediated by separase, an endopeptidase that cleaves the chromosomal cohesin SCC1. Separase is inhibited by securin, which is degraded at the metaphase-anaphase transition. Using Xenopus egg exts., we demonstrate that high CDC2 activity inhibits anaphase but not securin degrdn. We show that separase is kept inactive under these conditions by a mechanism independent of binding to securin. Mutation of a single phosphorylation site on separase relieves the inhibition and rescues chromatid sepn. in exts. with high CDC2 activity. Using quant. mass spectrometry, we show that, in intact

cells, there is complete phosphorylation of this site in metaphase and significant dephosphorylation in anaphase. We propose that separase activation at the metaphase-anaphase transition requires the removal of both securin and an inhibitory phosphate.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:786622 CAPLUS
DOCUMENT NUMBER: 136:98960
TITLE: Phosphorylation of the cohesin subunit Scc1 by Polo/Cdc5 kinase regulates sister chromatid separation in yeast
AUTHOR(S): Alexandru, Gabriela; Uhlmann, Frank; Mechtler, Karl; Poupart, Marc-Andre; Nasmyth, Kim
CORPORATE SOURCE: Res. Inst. of Mol. Pathol. (IMP), Vienna, A-1030, Austria
SOURCE: Cell (Cambridge, MA, United States) (2001), 105(4), 459-472
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB At the onset of anaphase, a caspase-related protease (**separase**) destroys the link between sister chromatids by cleaving the cohesin subunit Scc1. During most of the cell cycle, **separase** is kept inactive by binding to an **inhibitory protein** called securin. **Separase** activation requires proteolysis of securin, which is mediated by a ubiquitin **protein** ligase called the anaphase-promoting complex. Cells regulate anaphase entry by delaying securin ubiquitination until all chromosomes have attached to the mitotic spindle. Though no longer regulated by this mitotic surveillance mechanism, sister sepn. remains tightly cell cycle regulated in yeast mutants lacking securin. We show here that the Polo/Cdc5 kinase phosphorylates serine residues adjacent to Scc1 cleavage sites and strongly enhances their cleavage. Phosphorylation of **separase** recognition sites may be highly conserved and regulates sister chromatid sepn. independently of securin.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:756258 CAPLUS
DOCUMENT NUMBER: 136:306549
TITLE: Role of the kinetochore protein Ndc10 in mitotic checkpoint activation in Saccharomyces cerevisiae
AUTHOR(S): Fraschini, R.; Beretta, A.; Lucchini, G.; Piatti, S.
CORPORATE SOURCE: Dipartimento di Biotecnologie e Bioscienze, Universita degli Studi di Milano-Bicocca, Milan, 20126, Italy
SOURCE: Molecular Genetics and Genomics (2001), 266(1), 115-125
CODEN: MGGOAA; ISSN: 1617-4615
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mitotic checkpoints delay cell cycle progression in response to alterations in the mitotic app., thus ensuring correct chromosome segregation. While improper spindle orientation activates the Bub2/Bfa1-dependent checkpoint in budding yeast, delaying exit from mitosis, lack of bipolar kinetochore-microtubule attachment activates a signal transduction cascade that prevents both anaphase onset and exit from mitosis by **inhibiting** the Cdc20/APC (Anaphase Promoting Complex)-mediated proteolysis of securin and inactivation of mitotic cyclin-dependent kinases (CDKs), resp. Proteolysis of the securin Pds1 is necessary to liberate the **separase** Esp1, which then triggers sister chromatid sepn., whereas inactivation of mitotic CDKs is a prerequisite for exit from mitosis and for starting a new round of DNA replication in the next cell cycle. In budding yeast, this latter checkpoint response involves the **proteins** Mad1, 2, 3, Bub1 and

Bub3, whose vertebrate counterparts localize to unattached kinetochores. Mutations that alter other kinetochore **proteins** result in mitotic checkpoint activation, while the ndc10-1 mutation not only impairs kinetochore function, but also disrupts the checkpoint response, indicating a role for Ndc10 in this process. Here the authors present evidence that Ndc10 is not part of the Bub2/Bfa1-dependent pathway, and its role in the checkpoint response might also be different from that of the other Mad and Bub **proteins**. Indeed, Ndc10, unlike other mitotic checkpoint **proteins**, is not required for the mitotic block induced by over-expression of the Mps1 **protein** kinase, which is implicated in mitotic checkpoint control. Furthermore, the delay in mitotic exit caused by non-degradable Pds1, which does not require Mad and Bub **proteins**, depends on Ndc10 function. The authors propose that a pathway involving Ndc10 might monitor defects in the mitotic app. independently of the Mad and Bub **proteins**. Since the Esp1 **separase** is required for exit from mitosis in both ndc10-1 and nocodazole-treated mad2.DELTA. cells, the two signal transduction cascades might ultimately converge on the inactivation of Esp1.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT